



# NOTES

## HEPADNAVIRIDAE

### MICROBE OVERVIEW

- *Hepadnaviridae*: family of DNA viruses, causes liver disease
- Produces DNA polymerase with reverse transcriptase, RNase activity

#### Replication/multiplication

- Reverse transcription (RNA intermediate)

#### Structure

- Enveloped

- Icosahedral capsid
- Partially double stranded, partially single stranded circular DNA

#### COMPLICATIONS

- Chronic hepatitis, acute liver failure (fulminant hepatitis), liver cirrhosis, hepatocellular carcinoma (HCC)

## HEPATITIS B VIRUS

[osms.it/hepatitis-b-virus](https://osms.it/hepatitis-b-virus)

### **PATHOLOGY & CAUSES**

- Hepatitis B virus (HBV)
  - **DNA virus**: can cause acute/chronic liver disease
  - Member of *Hepadnaviridae* family (only human pathogenic species)
- **Target**: hepatocytes, zone I (periportal area)
- **Incubation period**: six weeks to six months

#### Antigens

- Hepatitis B surface antigen (HBsAg/ Australia antigen)
  - Key infection marker
- Hepatitis B core antigen (HBcAg)
  - Not detectable in serum; found in liver with acute/chronic hepatitis B
- Hepatitis B e antigen (HBeAg)
  - **Secreted by infected cells**; indicates active infection, replication

#### Transmission

- Perinatal (childbirth), parenteral (e.g. IV drug use, blood transfusions), **sexual**
- HBV survives  $\geq$  seven days in environment

#### Highest prevalence

- Parts of sub-Saharan Africa, mainly due to perinatal transmission
- Lower prevalence areas have greater association with parenteral, sexual transmission

### TYPES

#### Acute hepatitis

- Liver inflammation for < six months)
- HBV penetrates hepatocytes  $\rightarrow$  CD8+ T-lymphocyte activation  $\rightarrow$  cytotoxic killing  $\rightarrow$  hepatocyte apoptosis  $\rightarrow$  liver damage, inflammation
- Phases
  - Early, window (antigens undetectable), recovery

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- Acute liver failure progression: < 1%
- Chronic hepatitis progression (in adults): < 5%
- Acute liver failure
  - Acute liver injury (severe hepatocyte necrosis), hepatic encephalopathy, coagulopathy
  - Excessive immune response → massive hepatocyte lysis
  - Preexisting liver disease absence
  - Associated with HBV genotype D

### Chronic hepatitis

- HBsAg persistent for > six months
- Pathogenesis
  - HBV penetrates hepatocytes → insufficient CD8+ T-lymphocyte activation → “immune tolerance” → HBV persistence
- Progression to HCC
  - HBV integrates to host DNA → oncogene activation → **oncogenesis**
- Chronicity depends highly on age at time of infection
  - Younger age, ↑ chronicity risk
  - Immunosuppressed, elderly people also more susceptible
- Phases
  - **Immune tolerant**: no liver inflammation/fibrosis
  - **Immune active**: liver damage, inflammation, possible fibrosis
  - **Immune inactive**: ↓ inflammation
  - **Reactivation**: liver damage, inflammation, possible fibrosis
  - **“Recovery”**: occult HBV, HBsAg negative; still infected, disease inactive (best prognosis)

### RISK FACTORS

- IV drug use
- **Healthcare workers**
  - Frequent contact with blades, needles, body fluids
- High-risk sexual behavior
- Anal intercourse
- Previous HIV/hepatitis C infection

## COMPLICATIONS

- **HCC**, fulminant hepatitis, liver cirrhosis

### Hepatic encephalopathy

- Excessive nitrogen load, electrolyte disturbances → altered neurologic functions in individuals with severe liver disease

### Hepatorenal syndrome

- Portal hypertension → splanchnic vasodilation → ↓ effective circulatory volume → ↑ renin-angiotensin-aldosterone system → renal vasoconstriction → hepatorenal syndrome (liver dysfunction → kidney failure)

### Bleeding diathesis

- Hypocoagulability → ↑ hemorrhage risk

## SIGNS & SYMPTOMS

### Acute hepatitis

- Can be anicteric (not accompanied by jaundice) with non-specific symptoms (e.g. fever, malaise, nausea, vomiting)
- Some progress to icteric hepatitis with hepatomegaly, right upper-quadrant pain, **jaundice** (30%), dark-colored urine (due to conjugated hyperbilirubinemia), pale stool

### Chronic hepatitis

- Mostly asymptomatic/non-specific symptoms until late disease stages
- Exacerbations may present as acute hepatitis
- **Jaundice**, ascites, splenomegaly, encephalopathy (e.g. personality changes, ↓ level of consciousness, intellectual impairment, asterixis) may present
- Extrahepatic manifestations (occasionally)
  - Fever, rash, arthralgia, arthritis, glomerulonephritis

## DIAGNOSIS

### LAB RESULTS

- HBV DNA detection
  - Polymerase chain reaction (PCR), in-situ hybridization, Southern hybridization

**Laboratory testing**

- ↑ alanine aminotransferase (ALT), aspartate aminotransferase (AST)
  - ALT > AST
  - Usually ALT in acute hepatitis > 1000 U/L (may be ↓ in chronic hepatitis)
  - ALT levels take longer than AST to return to normal
- ↑ ALT for > six months indicates chronicity
- ↑ alpha-fetoprotein (AFP) in HCC
- Liver fibrosis
  - ↓ leukocytes, platelets
  - AST/ALT > 1 (normal ≈ 0,8)
  - ↑ total bilirubin
  - ↓ serum albumin
  - Delayed prothrombin time, ↑ international normalized ratio (INR)

**Serologic marker detection through enzyme immunoassay**

- Hepatitis B surface antigen (HBsAg)
  - Indicates infection (acute/chronic)
- Hepatitis B surface antibodies (Anti-HBs)
  - Provides HBV infection immunity
  - appears after vaccination/resolved acute hepatitis

- IgM antibodies against hepatitis B core antigen (IgM anti-HBc)
  - Acute infection/chronic hepatitis reactivation phase
- IgG antibodies against hepatitis B core antigen (IgG anti-HBc)
  - Non-specific antibody; may be ↑ during acute, resolved, chronic hepatitis
- Hepatitis B e antigen
  - Active replication, high infectivity
- Hepatitis B e antibodies
  - Low replication, infectivity

**Liver biopsy**

- Acute hepatitis
  - Mononuclear infiltrate
  - Pericentral inflammation, necrosis
  - Eosinophilic hepatocytes
- Chronic hepatitis
  - Fibrosis
  - Nodule formation
  - Mononuclear portal infiltrate
  - Some hepatocytes have uniformly dull cytoplasm due to endoplasmic reticulum swelling ("ground glass" hepatocytes)

**HEPATITIS B SEROLOGIC MARKERS**

|              | VACCINATION | ACUTE HEPATITIS | RESOLVED ACUTE HEPATITIS | CHRONIC HEPATITIS |
|--------------|-------------|-----------------|--------------------------|-------------------|
| HBsAg        | -           | +               | -                        | +                 |
| Anti-HBs     | +           | -               | +                        | -                 |
| IgM anti-HBc | -           | +               | -                        | -                 |
| IgG anti-HBc | -           | +               | +                        | +                 |
| HBeAg        | -           | +               | -                        | +/-               |
| Anti-HBe     | -           | +               | +                        | +                 |



**Figure 78.1** Ground glass hepatocytes seen in the liver of an individual with hepatitis B infection.

## TREATMENT

### MEDICATIONS

- Antiviral monotherapy
  - Severe acute hepatitis, pre-existing liver disease, concomitant hepatitis C/D infection, immunocompromised, elderly

#### Acute hepatitis

- Post-exposure prophylaxis
  - HBV vaccine and immunoglobulin

#### Chronic hepatitis

- Combination therapy (e.g. lamivudine, interferon)

### Prevention

- HBV vaccine
  - Recombinant type most commonly used
    - HBsAg inserted in yeast cells
- HBsAg → development of anti-HBsAg → HBV infection immunity
- Intramuscular administration
- Three doses for coverage (very effective)
- **Administration regime:** 0, 1–2 months, 6–12 months
  - *Infant immunization:* first dose at birth
  - Does not require booster dose (long-term protection)

### SURGERY

- Acute liver failure
  - Consider liver transplantation

### OTHER INTERVENTIONS

- Acute liver failure
  - Fluid resuscitation, early nutritional support, antiviral therapy (nucleoside/nucleotide analogues)

#### Acute hepatitis

- Supportive treatment (e.g. fluid therapy, nutrition)

# HEPATITIS D VIRUS

osms.it/hepatitis-d-virus

## **PATHOLOGY & CAUSES**

- **Hepatitis D virus (HDV/delta virus):** incomplete RNA virus; contributes to acute liver failure development, chronic hepatitis exacerbation in people coinfecting/ previously infected with HBV
- HDV not member of *Hepadnaviridae* family
- HDV infection inhibits HBV replication due to HBV, HDAg interaction during viral replication
  - **Coinfected individuals:** HDV predominant
  - ↑ inflammatory response (compared to HBV alone)
  - Poor response to existing HBV treatment
- Incubation period
  - 6–24 weeks

### **Structure**

- **Outer envelope made of HBsAg**, inner HDV RNA, delta antigen (HDAg)

### **Transmission**

- Parenteral, sexual, perinatal (very rare)

### **Satellite virus**

- Can only infect if host also infected with HBV
  - **Coinfection:** simultaneous infection
  - **Superinfection:** HDV infection after established HBV infection; **more severe**

## **RISK FACTORS**

- IV drug use, high-risk sexual behavior, HBV presence

## **SIGNS & SYMPTOMS**

### **Coinfection**

- Biphase course with **acute hepatitis symptoms**

### **Acute liver failure**

- Systemic symptoms
  - E.g. **fever**, malaise, nausea, vomiting)
  - Hepatomegaly, right upper quadrant pain; sometimes jaundice, dark colored urine, pale stool
- Hepatic encephalopathy
  - Personality changes, ↓ level of consciousness, intellectual impairment, asterixis

## **DIAGNOSIS**

### **LAB RESULTS**

- Serologic marker detection
  - IgM/IgG anti-HDV
- PCR assays
  - HDV RNA detection

## **TREATMENT**

### **MEDICATIONS**

- Pegylated interferon alpha
- Prevention
  - HBV vaccine

### **SURGERY**

- Consider liver transplantation for chronic hepatitis D, acute liver failure